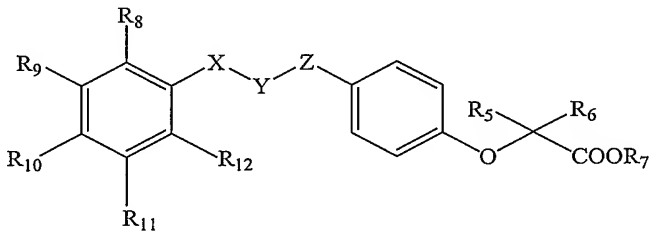
CLAIMS

1. A composition comprising an allosteric effector compound, which is substantially free of impurities wherein said allosteric effector compound is selected from the group of compounds having the following formula:



wherein

X and Z are independently selected from the group consisting of CH_2, CO, NH or O, and Y is selected from the group consisting of CO or NH, with the caveat that X, Y, and Z must all be different from each other;

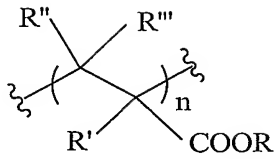
R_5 and R_6 are independently selected from the group consisting of hydrogen, halogen, substituted or unsubstituted C_{1-12} alkyl groups, carboxylic acid and ester groups, substituted or unsubstituted aromatic or heteroaromatic groups, or alkyl moieties of part of an aliphatic ring connecting R_5 and R_6;

R_7 is a selected from the group consisting of hydrogen, a cationic counterion, selected from the group consisting of sodium, potassium or ammonium, a metal, or a substituted or unsubstituted C_{1-6} alkyl group; and

R_{8-12} are independently selected from the group consisting of hydrogen, halogen, substituted or unsubstituted C_{1-3} alkyl groups, or alkyl moieties of an aromatic or aliphatic ring incorporating two of the R_{8-12} sites.

2. The composition of claim 1, wherein said impurities are selected from the group consisting of polymeric impurities and other related impurities selected from the group consisting of poly (ethyl methacrylate) (PEM), 3-monomethyl efaproxiral (3MMRS13), α-desmethyl efaproxiral (DDMRS13), monomethyl α to COOH (DMRS13), 3,4-dimethyl efaproxiral (3,4DMRS13), α-ethyl- efaproxiral, diacid (DA), 3,5-dimethyl aniline (3,5-DMA), amidophenol and the ethyl ester of efaproxiral.

3. The composition of claim 2, wherein said impurity is a polymeric impurity selected from the group of compounds having the following structure:



wherein

R, R', R" and R''' are independently selected from the group consisting of substituted or unsubstituted C_{1-12} alkyl group, hydrogen, halogen, a carboxylic acid or ester group, and a substituted or unsubstituted heteroaromatic group; and

n is any number of units appropriate for a polymer of repeating units.

4. The composition of claim 3, wherein R' is selected from a substituted or unsubstituted C_{1-3} alkyl group and R is a methyl or ethyl group.

5. The composition of claim 2, wherein said polymeric impurity is poly (ethyl methacrylate) (PEM).

6. The composition of claim 3, wherein said polymeric impurity is present in the composition at less than about 500 ppm.

7. The composition of claim 3, wherein said polymeric impurity is present in the composition at less than about 200 ppm.

8. The composition of claim 3, wherein said polymeric impurity is present in the composition at less than about 100 ppm.

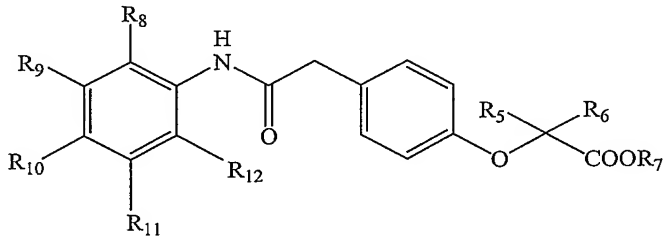
9. The composition of claim 3, wherein said polymeric impurity is present in the composition at less than about 80 ppm.

10. The composition of claim 3, wherein said polymeric impurity is present in the composition at less than about 10 ppm.

11. The composition of claim 2, wherein said related impurities are each present in the composition at less than about 1000 ppm.

12. The composition of claim 2, wherein said related impurities are each present in the composition at less than about 500 ppm.

13. The composition of claim 1, wherein said allosteric effector compound is selected from the group of compounds having the following chemical structure:



wherein

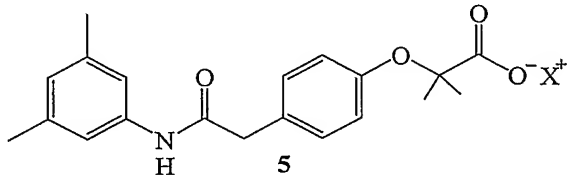
R_5 and R_6 are independently selected from the group consisting of hydrogen, halogen, substituted or unsubstituted C_{1-12} alkyl groups, carboxylic acid and ester groups, substituted or unsubstituted aromatic or heteroaromatic groups or alkyl moieties of part of an aliphatic ring connecting R_5 and R_6;

R_7 is a selected from the group consisting of hydrogen, a cationic counterion, selected from the group consisting of sodium, potassium or ammonium, a metal, or a substituted or unsubstituted C_{1-6} alkyl group; and

R_{8-12} are independently selected from the group consisting of hydrogen, halogen, substituted or unsubstituted C_{1-3} alkyl groups or alkyl moieties of an aromatic or aliphatic ring incorporating two of the R_{8-12} sites.

14. The composition of claim 13, wherein R_5 and R_6 are independently selected from H or CH_3 and R_7 is selected from hydrogen or a cationic counterion.

15. The composition of claim 1, wherein said allosteric effector compound is 2-[4-((((3,5-dimethylphenyl)amino)carbonyl)methyl)phenoxy]-2-methyl propionic acid (efaproxiral) (**5**)



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wherein X is selected from the group consisting of H or a cationic counterion selected from the group consisting of sodium, potassium or ammonium.

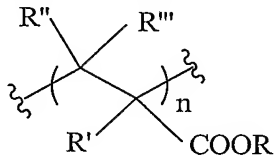
16. A method for the preparation of a composition comprising an allosteric effector compound that is substantially free of polymeric impurities said method comprising the steps of:

a) coupling a substituted aniline with 4-hydroxyphenylacetic acid to yield the corresponding substituted phenol;

b) adding the product of step (a) to an alkyl ester halide to yield a substituted ethyl ester; and

c) saponifying the substituted alkyl ester to provide the salt of the acid, wherein all steps are performed in a reaction vessel that does not contain metals that promote the formation of polymeric byproducts.

17. The method of claim 16, wherein said polymeric impurity is selected from the group of compounds having the following structure:



wherein

R, R', R" and R''' are independently selected from the group consisting of substituted or unsubstituted C_{1-12} alkyl group, hydrogen, halogen, a carboxylic acid or ester group, and a substituted or unsubstituted heteroaromatic group; and

n is any number of units appropriate for a polymer of repeating units.

18. The method of claim 17, wherein R' is independently selected from a substituted or unsubstituted C_{1-3} alkyl group and R is a methyl or ethyl group.

19. The method of claim 16, wherein said polymeric impurity is poly (ethyl methacrylate) (PEM).

20. The method of claim 16, wherein said polymeric impurity is present in the composition at less than about 500 ppm.

21. The method of claim 16, wherein said polymeric impurity is present in the composition at less than about 200 ppm.

22. The method of claim 16, wherein said polymeric impurity is present in the composition at less than about 100 ppm.

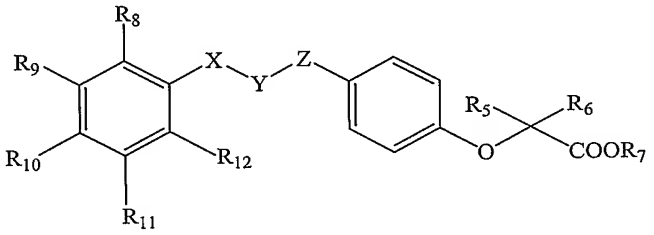
23. The method of claim 16, wherein said polymeric impurity is present in the composition at less than about 80 ppm.

24. The method of claim 16, wherein said polymeric impurity is present in the composition at less than about 10 ppm.

25. The method of claim 16, wherein said reaction vessel is selected from the group consisting of glass lined stainless steel (SS), passivated stainless steel, Hastelloy® or similar alloys.

26. The method of claim 16, wherein said reaction vessel is selected from a Hastelloy 276® reactor or a SS (316) reactor.

27. The method of claim 16, wherein said allosteric effector compound is selected from the group of compounds having the following formula:



wherein

X and Z are independently selected from the group consisting of CH_2, CO, NH or O, and Y is selected from the group consisting of CO or NH, with the caveat that X, Y, and Z must all be different from each other;

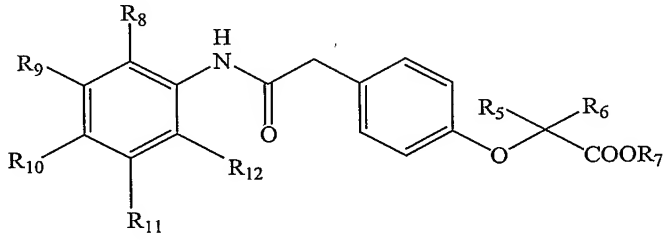
R_5 and R_6 are independently selected from the group consisting of hydrogen, halogen, substituted or unsubstituted C_{1-12} alkyl groups, carboxylic acid and ester groups, substituted

or unsubstituted aromatic or heteroaromatic groups, or alkyl moieties of part of an aliphatic ring connecting R_5 and R_6;

R_7 is a selected from the group consisting of hydrogen, a cationic counterion, selected from the group consisting of sodium, potassium or ammonium, a metal, or a substituted or unsubstituted C_{1-6} alkyl group; and

R_{8-12} are independently selected from the group consisting of hydrogen, halogen, substituted or unsubstituted C_{1-3} alkyl groups, or alkyl moieties of an aromatic or aliphatic ring incorporating two of the R_{8-12} sites.

28. The method of claim 27, wherein said allosteric effector compound is selected from the group of compounds having the following chemical structure:



wherein

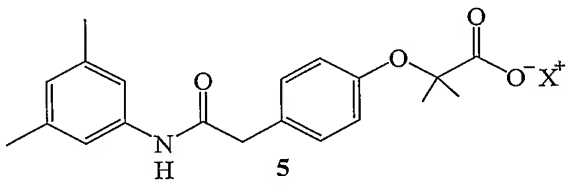
R_5 and R_6 are independently selected from the group consisting of hydrogen, halogen, substituted or unsubstituted C_{1-12} alkyl groups, carboxylic acid and ester groups, substituted or unsubstituted aromatic or heteroaromatic groups or alkyl moieties of part of an aliphatic ring connecting R_5 and R_6;

R_7 is a selected from the group consisting of hydrogen, a cationic counterion, selected from the group consisting of sodium, potassium or ammonium, a metal, or a substituted or unsubstituted C_{1-6} alkyl group; and

R_{8-12} are independently selected from the group consisting of hydrogen, halogen, substituted or unsubstituted C_{1-3} alkyl groups or alkyl moieties of an aromatic or aliphatic ring incorporating two of the R_{8-12} sites.

29. The method of claim 28, wherein R_5 and R_6 are independently selected from H or CH_3 and R_7 is selected from hydrogen or a cationic counterion.

30. The method of claim 28, wherein said allosteric effector compound is 2-[4-((((3,5-dimethylphenyl)amino)carbonyl)methyl)phenoxy]-2-methyl propionic acid (efaproxiral) (**5**)



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wherein X is selected from the group consisting of H or a cationic counterion selected from the group consisting of sodium, potassium or ammonium.

31. The method of claim 16, wherein said method further comprises extracting the product of step (c) with a solvent selected from the group consisting of methyl isobutyl ketone, isopropyl acetate, ethyl acetate, methyl ethyl ketone, chlorinated solvents selected from the group consisting of chloroform and methylene chloride at least once.

32. The method of claim 31, wherein said extraction is performed two times.

33. The method of claim 16, wherein said method further comprises recrystallization of the product of step (c) in an appropriate solvent.

34. The method of claim 33, wherein said solvent is selected from the group consisting of ethanol and acetone and mixtures of acetone/ethanol, acetone/methanol and ethanol/methanol/acetone/water.

35. The method of claim 16, wherein said method further comprises extracting the product of step (c) with an appropriate solvent, followed by recrystallization of the extracted product.

36. The method of claim 16, wherein said method further comprises extracting the product of step (c) with an appropriate solvent, followed by recrystallization of the extracted product and filtration of the recrystallized product.

37. The method of claim 36, wherein said filtration is performed using a polymeric filter selected from the group consisting of poly(vinylidene difluoride) (PVDF) or a cellulose ester filter.

38. The method of claim 38, wherein said polymeric filter is PVDF.

39. A product prepared according to the method of claim 16.

40. A product prepared according to the method of claim 35.

41. A product prepared according to the method of claim 36.

42. A method for preparing a composition of the allosteric effector compound efaproxiral-Na that is substantially free of polymeric impurities said method comprising the steps of:

a) reacting a solution of 4-hydroxyphenylacetic acid with 3,5-dimethylaniline to yield amidophenol;

b) reacting the product of step (a) with ethyl 2-bromoisobutyrate to yield the ethyl ester; and

c) saponifiying the product of (b) to yield a carboxylic acid salt, wherein all steps are performed in a reaction vessel that does not contain metals that promote the formation of polymeric byproducts.

43 The method of claim 42, wherein said reaction vessel is selected from a Hastelloy 276® reactor, a SS (316) reactor or a glass lined SS reactor.

44. The method of claim 42, wherein said method further comprises extracting the product of step (c) with a solvent selected from the group consisting of methyl isobutyl ketone, isopropyl acetate, ethyl acetate, methyl ethyl ketone, chlorinated solvents selected from the group consisting of chloroform and methylene chloride at least once.

45. The method of claim 44, wherein said extraction is performed two times.

46. The method of claim 42, wherein said method further comprises recrystallization of the product of step (c) in an appropriate solvent.

47. The method of claim 46, wherein said solvent is selected from the group consisting of ethanol and acetone and mixtures of acetone/ethanol, acetone/methanol and ethanol/methanol/acetone/water.

48. The method of claim 42, wherein said method further comprises extracting the product of step (c) with an appropriate solvent, followed by recrystallization of the extracted product and filtration of the recrystallized product.

49. The method of claim 48 , wherein said filtration is performed using a polymeric filter selected from the group consisting of PVDF or a cellulose ester filter.

50. The method of claim 49 wherein said polymeric filter is PVDF.

51. A product prepared according to the method of claim 42.

52. A product prepared according to the method of claim 48.

53. A method for the preparation of efaproxiral-Na (**5**) compound of formula that is substantially free of impurities, said method comprising the steps of:

a) reacting a solution of 4-hydroxyphenylacetic acid with 3,5-dimethylaniline to yield amidophenol;

b) reacting the product of step (a) with ethyl 2-bromoisobutyrate to yield the ethyl ester;

c) saponifiying the product of (b) to yield a carboxylic acid salt; and

d) extracting the product of step (c) with an appropriate solvent at least one time,

wherein all steps are performed in a reaction vessel that does not contain metals that promote the formation of polymeric byproducts.

54. The method of claim 53, wherein the impurity is a polymeric impurity.

55. The method of claim 54, wherein said polymeric impurity is present in the composition at less than about 100 ppm.

56. The product prepared according to the method of claim 53.

57. A method for the preparation of efaproxiral-Na (**5**) compound of formula that is substantially free of impurities, said method comprising the steps of:

a) reacting a solution of 4-hydroxyphenylacetic acid with 3,5-dimethylaniline to yield amidophenol;

b) reacting the product of step (a) with ethyl 2-bromoisobutyrate to yield the ethyl ester;

c) saponifiying the product of (b) to yield a carboxylic acid salt;

d) extracting the product of step (c) with an appropriate solvent at least one time, and

e) recrystallizing the product of step (d) in an appropriate solvent,

wherein all steps are performed in a reaction vessel that does not contain metals that promote the formation of polymeric byproducts.

58. The method of claim 57, wherein the solvent of step (d) is MIBK and the solvent of step (e) is selected from ethanol and/or acetone.

59. The method of claim 57, wherein said polymeric impurity is present in the composition at less than about 100 ppm.

60. The product prepared according to the method of claim 57.

61. A method for the preparation of efaproxiral-Na (**5**) compound of formula that is substantially free of impurities, said method comprising the steps of:

a) reacting a solution of 4-hydroxyphenylacetic acid with 3,5-dimethylaniline to yield amidophenol;

b) reacting the product of step (a) with ethyl 2-bromoisobutyrate to yield the ethyl ester;

c) saponifiying the product of (b) to yield a carboxylic acid salt;

d) extracting the product of step (c) with an appropriate solvent at least one time;

e) recrystallizing the product of step (d) in an appropriate solvent; and

f) filtering the product of step (e) with a filter that removes polymeric impurities,

wherein all steps are performed in a reaction vessel that does not contain metals that promote the formation of polymeric byproducts.

62. The method of claim 61, wherein the solvent of step (d) is MIBK, the solvent of step (e) is selected from ethanol and/or acetone and the polymeric filter of step (f) is PVDF.

63. The method of claim 61, wherein the solvent of step (d) is MIBK, the solvent of step (e) is selected from ethanol and/or acetone and the polymeric filter of step (f) is modified cellulose.

64. A product prepared according to the method of claim 62.

65. A method for analyzing a composition comprised of an allosteric hemoglobin modifier compound said method comprising the steps of:

a) pyrolyzing said composition;

b) analyzing said pyrolyzed product by gas chromatography/mass spectrometry (GC/MS).

66. The method of claim 65 further comprising the step of adding an internal standard to the composition prior to step a).

67. The method of claim 66 wherein said internal standard is labeled with an isotope.

68. The method of claim 67 wherein said internal standard is labeled with an isotope of an atom selected from the group consisting of hydrogen, carbon, oxygen and nitrogen.

69. The method of claim 67 wherein said isotope is selected from the group consisting of deuterium (D), carbon 13 (^{13}C), oxygen 18 (^{18}O) and nitrogen 15 (^{15}N).

70. The method of claim 67 wherein said isotopically labeled internal standard is deuterated PEM.